REGULATORY FOCUS

Human microbiomes in health and disease: Strategic options for regulatory science and healthcare policy

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This article describes the human microbiota and microbiomes' strategic role in personalizing health and disease management, which is rapidly demanding diligent regulatory science and policy action to ascertain confidence and trust among consumers, patients, and healthcare providers. The authors discuss why establishing harmonized processes and standards to better understand the baseline healthy microbiota is essential to development of strategies for nutrition and clinical applicability. They conclude that, given the complexity of issues, a well-orchestrated, multistakeholder approach is advisable for the best chance of success.

Introduction

Traditional paradigms for healthcare product development are significantly challenged as we enter an era of new tools (e.g., CRISPR, RNAi, "omics" diagnostic technologies, in silico trials, digitization, apps, and wearables) and face new or shifting targets, such as human microbiota/microbiomes, consumer-patient continuum, and shifts from disease management to health-preserving strategies. In addition to current population-based approaches, rapidly evolving science and technologies provide the potential for personalizing nutrition and medicine, leading toward highly individualized, precision therapies

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and preventive medicine. These developments are opening new avenues to tackle rare (orphan) and common noncommunicable and communicable diseases.[1-3]

Targeting microbiomes on and in humans as part of developing health- and disease-focused solutions for the human organism opens a broad perspective for preventative, as well as therapeutic, interventions. The human microbiota – at times considered a virtual organ constituted of eubacteria, as well as archaea, filamentous fungi, yeasts, protozoa, viruses – cohabits our bodies and may hold the key to many aspects of maintaining good health. These aspects include having an impact on digestion and boosting the immune system, cognitive functions, and even longevity. Multiple facts and causalities have yet to be established or refined because it is still not clear what defines a healthy microbiome and what causal relationships exist between diet, health, disease, and respective disturbances.[4,5]

These opportunities and challenges require significant and acute out-of-the-box rethinking, as well as open communication and sharing of, and access to, data. It requires collaboration between multiple stakeholders from regulatory authorities, academia, manufacturers, healthcare professionals, payers, and patients to establish, interpret, and implement appropriate regulations and healthcare policies.[6]

Innovating regulatory science

Evolving scientific and innovative technological tools, processes, and respective terminologies, allow us to study and establish new personalized, precision, tailored, or bespoke approaches to preventing and treating diseases. All those elements will result in increased intervention efficiency compared with more general, less precise population-based approaches. With a focus on the human microbiome, a thorough knowledge of the types and ratios of microbes is needed before microbiome science can be incorporated into routine clinical practice.[7] There have been multiple efforts to establish the baseline(s) and standards for comparison of an individual's microbiome or metagenome to expand the knowledge base of what a 'normal' microbiome constitutes. These efforts still focus mostly on specific subsets of the issue, such as the Genomic Standards Consortium[8] on reporting (meta)genomic sequences, the Critical Assessment of Metagenomic Interpretation on computational tools used in metagenomic research,[9] or the International Human Microbiome Standards on standardization of procedures to study the gut microbiome.[10] Standardization is shown to be an issue for all microbiome research, as evidenced recently by MicrobiomeSupport on food systems microbiomes.[11-13]

It is essential to define which factors determine a healthy state of a particular microbiome and its resilience. Study results may lead to divergent conclusions, depending on the kinds of methods or procedures used. For example, various DNA extraction methods or the relative abundance of species (i.e., eubacteria, archaea, filamentous fungi, yeasts, protozoa, viruses) may favor different organisms and bias outcomes. Hence, agreements on human reference microbiomes and standardization of the various steps in microbiome analyses

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are needed for analyses linked to health, disease, or gender, or for comparing the clinical effects related to nutrition or drugs. More accurate, higher-throughput data accrual, and the ability to organize, store, access, and share data sets via comparable bioinformatics pipelines are needed to increase comparability and reproducibility of results.[14,15]

Standardization of the microbiome research field starts with the general adoption of standardized reference reagents. The UK's National Institute for Biological Standards and Control for microbiome analysis by next-generation sequencing DNA reference reagents were used to develop a first set of reference reagents and a four-measure framework for evaluating bioinformatics tool and pipeline bias. These can act as global working standards and will be evaluated as candidate World Health Organization International Reference Reagents.[16]

There has been progress in defining reference genomes reflecting the human gastrointestinal microbiome. A unified sequence catalog of more than 200,000 genomes and 171 million protein sequences of the human gut microbiome have been generated. Of note is that more than 70% of the species in the catalog have not yet been cultured, and 40% of the proteins have unknown functions. The catalog will be instrumental in gaining a deeper mechanistic understanding of the human gut microbiomes.[17]

With further standardization and the identification of reference metagenomes, the overall aim of a planned European coordination and support action[18] is to structure the field of microbiome research as related to human health and to reach global agreement, among scientific institutions, regulatory authorities, industry, and funders, on human reference microbiomes in an effort to:

- standardize the different steps in human microbiome studies
- define healthy states in and on the human body
- contribute to collaborative synergistic collection of microbiome data to improve coherence and reduce overlap
- integrate metagenomics and human microbiome references into other multilateral cooperation areas or personalized medicine approaches

There is a strategic role and potential of the human microbiome in personalizing health and disease management. A growing body of evidence suggests that noncommunicable diseases (NCDs) are associated with unbalanced dietary patterns and subsequent disturbances in the gut microbiome (dysbiosis), now recognized as an important biological interface between human genetics, lifestyle, and environmental conditions. With new research insight as a result of high throughput omics technologies in the current postgenomic era, there is growing interest in the functioning of the gut microbiome and the potential for developing innovative applications and personalized health solutions that target the microbiome.[19,20]

There is a need for diligent regulatory and policy action, considering the rapid pace of science and technology development and the application potential of

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these fields. A range of microbiome-related, or pre- and probiotics-based, products and derived active compounds (postbiotics) are already available, ranging from certain foods, to food supplements, including fermented foods or fermentation products, to fecal microbiota transplants (FMT). As with all healthcare-related products for nutritional or medicinal purposes, quality, safety, efficacy, and fitting the intended use or health claim must be demonstrated. However, current regulatory guidance is limited, because no consolidated national or global regulatory frameworks are applicable.[21] The need for an international dialogue between multiple stakeholders has been recognized for harmonizing the scientific standardization and technological development, as has the need for microbiome product regulation.[22] There is an ongoing dialogue among the Intestinal Microbiome-based Medicines European Task Group,[23] the International Probiotics Association,[24] and the Microbiome Therapeutics Innovation Group.[25]

The US Food and Drug Administration (FDA) has published guidance dedicated to FMT[26] and live-biotherapeutic products.[27] To further microbiome-related discussion and research, an interagency Microbiome Working Group was created as well, with FDA and National Institutes of Health experts. As Rousseau and colleagues have noted,[28] FMTs illustrate the variety of regulatory statuses potentially applicable to microbiome-related health products, some of which may conflict with existing regulations applicable to tissues and cells as defined in the EU and the US as "human material."[29,30] When administered for difficult-to-treat, potentially life-threatening Clostridium difficile infection, FMT meets the US definition of a biological product.[31] The EU Commission, without a specific framework, considers FMT as substances of human origin,[32] whereas some EU member states regulate FMT under tissues and cells standards and others as medicinal, non-ATMPs [advanced therapy medicinal products], or as foods.[33]

The nonclinical to clinical translation for microbiome-based products provides specific development challenges not typically encountered with other types of regulated healthcare products.[34] Given a large variety and mode of action, as well as the need for microbial characterization, a case-by-case product development approach is typical. Rousseau and colleagues[35] have described a vast spectrum of available microbiome-adapted nonclinical models, some of which are already well developed and continuously improving. Moreover, the regulatory framework for computer-based, in silico modelling and simulation, is starting to evolve and will eventually provide additional "digital evidence" to complement nonclinical and clinical studies. Rousseau and colleagues had also reviewed the potential use of in silico analyses in the microbiome field to investigate the interactions and role of the host microbiome on the host health,[36] explore the microbiomes' impact on the immune system, or identify personalized microbiota.[37,38]

Meeting the challenges of translating nonclinical models to the human situation, that is, moving models from bench to bedside, requires understanding of what determines a healthy microbiome, what a healthy reference microbiome is, and how microbiomes react to drugs and stimuli. Most drugs directly target a patient's cells or tissues, whereas microbiome-based products aim to modify,

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are modified by, or interact with the patient's microbiota. By the same token, microbiome–drug interactions and the resulting clinical responses linked to different gut microbiomes composition must be considered.[39] An integrative approach is advisable in regard to chemistry, manufacturing, and controls, or CMC, whereas nonclinical and clinical product development must align findings and increase their relevance toward expected human treatment outcomes.[40]

The food- and nutrition-related regulatory science framework for microbiome-based products is significantly less developed than it is for personalized, precision, or bespoke medicine. Beyond fulfilling potential novel food approval requirements for innovative components, "prebiotic," "probiotic," and "postbiotic" statements are considered implicit references to general, nonspecific benefits of the nutrient or food for overall good health or health-related well-being. They face the challenge of being accompanied by a specific, authorized health claim in the EU.[41,42]

The foremost mandate for regulatory science is to ensure consumer and patient safety in our volatile, uncertain, complex, ambiguous environment. Novel, rapidly evolving science and diagnostic technologies, of particular relevance for the microbiome, require regulatory science to enable a pragmatic shift of past paradigms.[43] Indeed, as omics technologies blur the traditional segmentation between consumers (health) versus patients (disease), disease prevention versus treatment, and nutrition versus drug, the regulatory framework should adopt this development as part of a new concept that approaches health holistically. In addition, although it is necessary to address the increased complexity of understanding and defining "where health ends and disease starts," practical solutions should include a certain level of uncertainty, while ensuring safety and efficacy of interventions.[44]

It is a challenge to provide healthcare solutions as rapidly as possible to citizens who need them urgently and would otherwise suffer unduly. Meeting the challenge requires a pragmatic rethinking and refinement of healthcare development and access approaches, involving diverse stakeholders from science, the healthcare profession, and industry, as well as payers and politicians. Recognizing this raises the question of what policymaking would be required to ensure a clinically beneficial and cost-efficient healthcare environment for the individual and the population.[45]

Innovating healthcare policy

Schneeman[46] has argued that, although science is necessary for developing policy, it is not always sufficient. For instance, challenges associated with disease prevention or global malnutrition problems will have to be addressed through multidisciplinary approaches. There have been multiple efforts to review current policies and the need to adapt to fast-moving, innovative areas, such as personalizing healthcare,[47] making sense of dietary guidelines,[48,49] creating and improving the evidence for nutrition,[50,51] and understanding and targeting the microbiome.[52,53]

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Given the developmental speed of new data and technologies, and the complexity and importance of nutrition products for life and healthcare, it might be necessary to factor in a certain amount of risk when building evidence for nutrition products – as well as the microbiota.[54,55] While justifying potential risk, the principle safety and utility of nutrition products for the prevention and management of diseases compared with other available healthcare options, cannot be overly emphasized.

Key issues expected to be addressed by the European coordination and support action referred to previously in this article, are essential for society and necessitate sound and rapid regulatory answers. In addition to the question of what constitutes a healthy state microbiome, we need to understand how to define health and disease in general, and, in that context, how to define who is a consumer and who is a patient. The new tools in science, as well as societal needs, such as NCD prevention or healthcare cost efficiency, require deeper investigation, which could result in some existing models and paradigms being questioned and having to be re-conceptualized or revised.[56] There is proven precedence in healthcare – for example, with the Orphan Disease Act – to create incentives to treat rare diseases, as with the development and approval pathways to respond to treatment challenges in the early days of the HIV/AIDS crisis, or with biotechnological versus small-entity chemical drugs.[57] New tools, targets, and an increasing cost burden, require similar action as quickly as possible.

The Organisation for Economic Co-operation and Development has clearly stated the key policy challenges for innovation in the microbiome through diet.[58] There is accumulating scientific evidence that the gut microbiome can be altered to generate greater health and well-being, offer better protection and resilience against NCDs, and even cure conditions such as type 2 diabetes and Clostridium difficile infections. Yet, to lead to innovative applications, science and innovation policies must be improved in five areas:

- science policy
- enabling translational science
- public–private collaboration
- regulatory frameworks
- skills, communication, and public awareness

The same principles should apply to the other microbiomes in and on the human body, even if less is known about them, compared with the gut, and they are not as widely researched.

Hence, beyond continuing to corroborate the foundation of well-known, population-based approaches, establishing the right framework conditions is essential when targeting the microbiome as part of personalized and preventive healthcare. A reliable and trustworthy science base is a major criterion for healthcare systems to support novel interventions or to take up in novel dietary guidelines. These should be supported by regulatory systems that accept the concept of a continuum between health and disease and food or drug and

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address these issues with a holistic approach. Creating awareness and value for citizens and healthcare providers is essential. However, it is important to not encourage the "hype" currently associated with areas of personalized nutrition and the microbiome (**Table**).[59]

TABLE Microbiomes and healthcare policy: Regulatory needs, creating value

Regulatory needs • Ensure the science base: Regulatory/legislative framework need to move with science at similar pace. • Harmonization and flexibility of regulatory frameworks: Cross-border solutions – use a common language. • Address the reality of the continuum (e.g., safety, evidence, documentation, speed): Health vs. disease; food vs. drug; consumer vs. patient; personalized vs. population-based approaches. • Outcome benefits: Allow for an acceptable level of scientific uncertainty in decision making.
Creating value • Cost and reimbursement mechanisms: To support development of personalized nutrition for health and disease prevention, and as part of preventive medicine. • Awareness creation: Getting the right message to the public and healthcare providers to: o move from hype to reality o agree on opportunities o translate knowledge and disseminate it o implement policies and solutions rapidly o provide dedicated training for healthcare professionals.

Given the strong evidence that microbiomes play an important role in human health and have clear links to many of the major NCDs, and possibly even in infectious diseases, it is of paramount importance that information is gathered, disseminated, and translated into policy solutions as quickly as possible. Due to their intrinsic complexities, these issues are best addressed through a well-managed, multistakeholder approach. The approach should be global, as well as regional and local, where advisable.

Multistakeholder campaigns[60]

Changes in science and technology are moving at unprecedented speed. Science is entrenched in thematic "silos" and struggling to cope with change, but it is needed for guiding regulatory and policymaking decisions.[61] The stakes are high for the ambitious goal of including the microbiome in our global healthcare approaches as soon as possible, and strengthening nutrition and personalized medicine as a beneficial and cost-effective way to prevent and/or treat NCDs.

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For sustained impact, a science-based, multistakeholder collaboration is the most promising and systematic way of finding comprehensive solutions to characterize the microbiota on a global scale and discern what determines a healthy microbiome in terms of aging, gender, and ethnicities. Given the enormity of the task and the many factors that can affect its trajectory, single-sector or stakeholder actions are unlikely to effectively influence all aspects of microbiome research in a coordinated fashion.[62,63]

Working together will maximize impact. Aligning goals, resources, and working in a coordinated manner, can multiply the impact of individual stakeholders. Exploring mutually beneficial linkages across stakeholders and programs can build organizational capacity. A multistakeholder approach, aligned with straightforward goals and a clear path to implementation, means pooling limited resources and allowing the collaboration to maximize financial and technical expertise. By working together, stakeholders can draw on collective core competencies to create a more comprehensive set of capabilities.[64]

The multistakeholder initiatives outlined in the preceding section, "Innovating regulatory science," provide insight into the state of research on the human microbiome and its links to health and certain diseases. In the best case scenario, they ultimately will establish a "community of practice" incorporating science, regulatory and industry experts, funders, and political leaders from around the globe, all addressing the need for standardization and agreeing on reference human microbiomes (in and on the human body) and how they relate to health, different disease areas, nutrition, gender differences, populations, and ethnicities.

Key will be to translate this knowledge from bench to bedside, thereby ensuring that the human microbiome awareness and information will reach healthcare professionals and the broader audience for rapid implementation. The Optimal Nutrition Care for All, or ONCA, multistakeholder campaign, spearheaded by the European Nutrition for Health Alliance, showcases a successful way forward in its efforts to tackle the costly malnutrition epidemic by implementing routine nutrition risk screening, increasing education campaigns to raise public awareness, and implementing proper science-based nutrition care for patients in 18 countries.[65,66] As an African proverb advocates: "If you want to go fast, go alone, if you want to go far, go together."[67]

Conclusion

The human microbiota and microbiomes play a strategic role in general population-based approaches as well as personalizing health and disease management. New evidence and the scourge of NCDs are demanding diligent regulatory science and rapid policy action to translate knowledge and disseminate and implement solutions rapidly to consumers, patients, and healthcare providers. Given the intrinsic complexity of challenges, issues are best addressed by a well-orchestrated, multistakeholder approach. While multiple analytical approaches are currently used by researchers worldwide, establishing basic harmonized processes and standards to better compare and understand the baseline healthy microbiota is essential for developing

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strategies for nutrition, personalized and preventive interventions, and clinical applicability.

Abbreviations

ATMP, advanced therapy medicinal product; **CMC,** chemistry, manufacturing, and controls; **CRISPR,** clustered regularly interspace short palindromic repeats; **FDA,** [US] Food and Drug Administration; **FMT,** fecal microbiota transplants; EU, European Union; **NCD,** noncommunicable disease; **RNAi,** RNA interference; **UK,** United Kingdom; **US,** United States.

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